

ToxCast™: A New Paradigm for Predicting Hazard and Prioritizing Toxicity Testing

*EPA Science Forum
23 May 2007*

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY



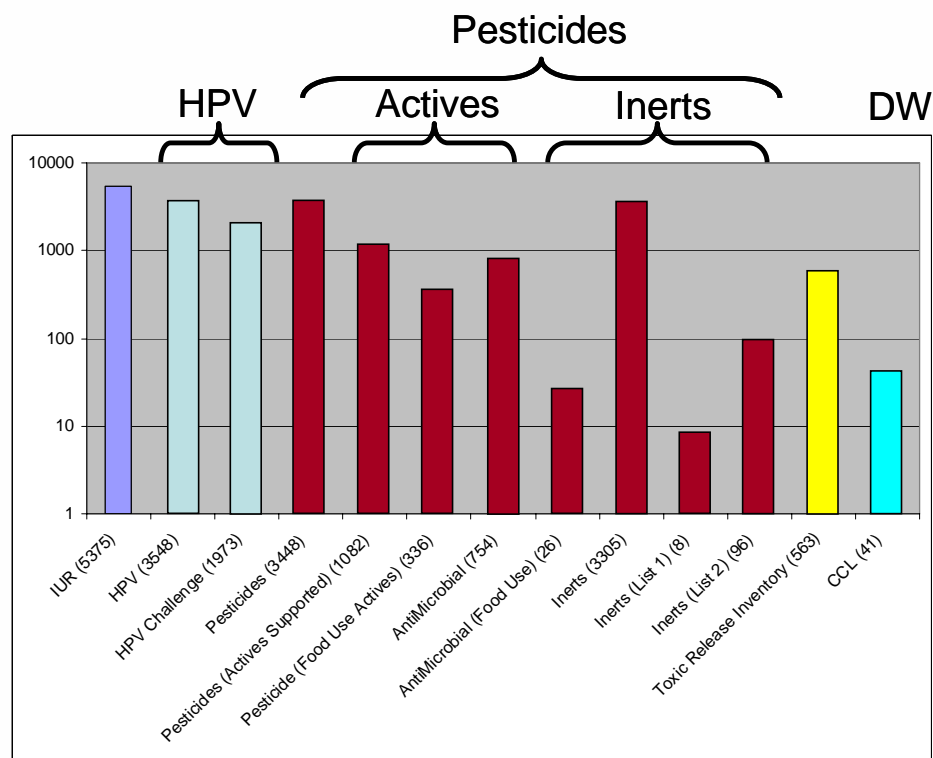
Keith Houck

Office of Research and Development
National Center for Computational Toxicology

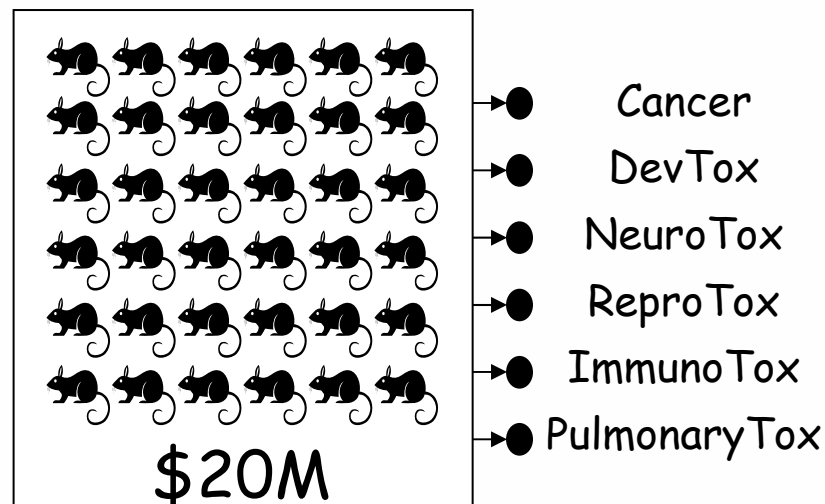
June 5, 2007

ToxCast™ Addresses the Critical Need for Prioritization

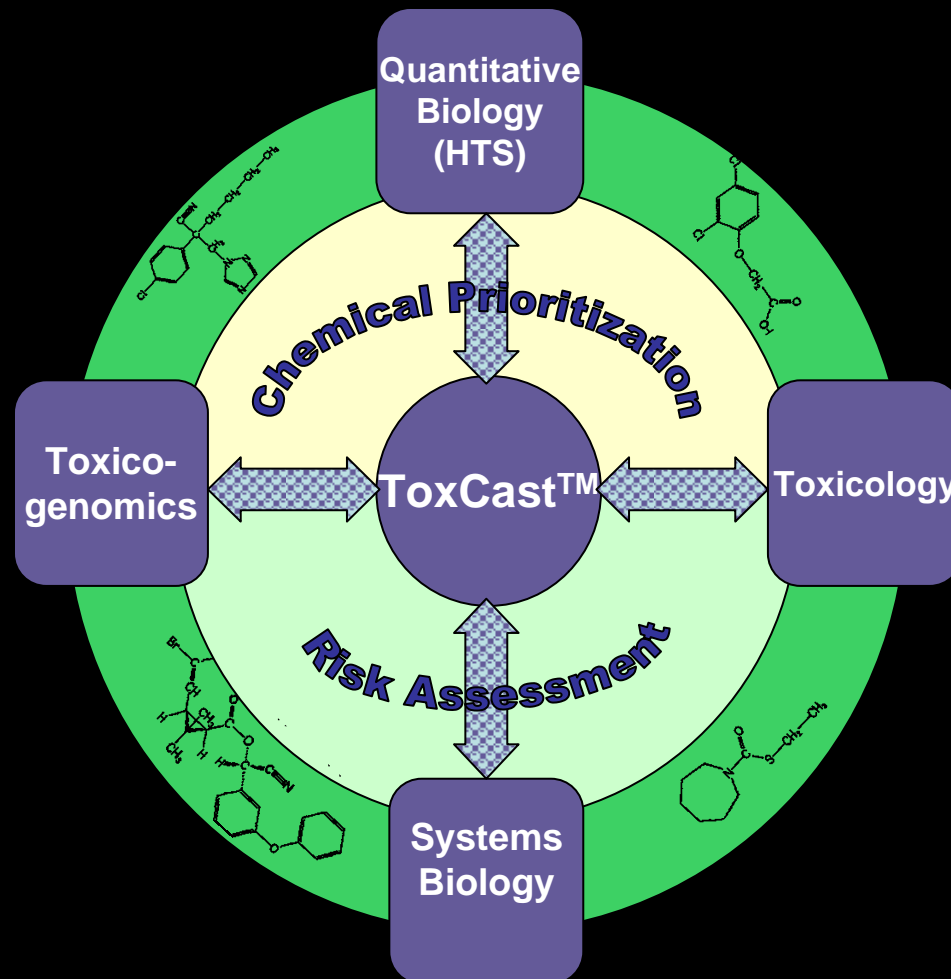
Too Many Chemicals



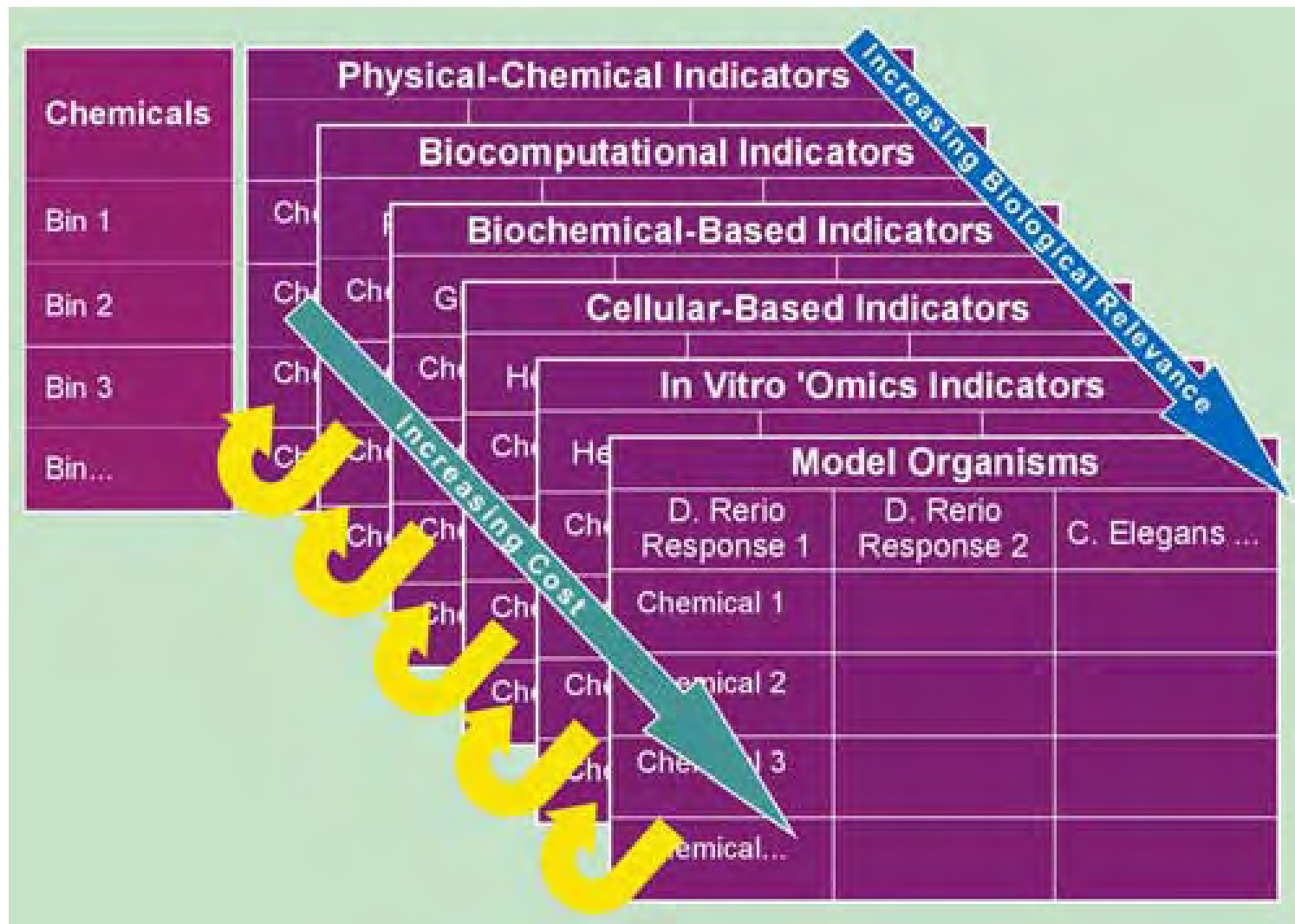
Too High a Cost



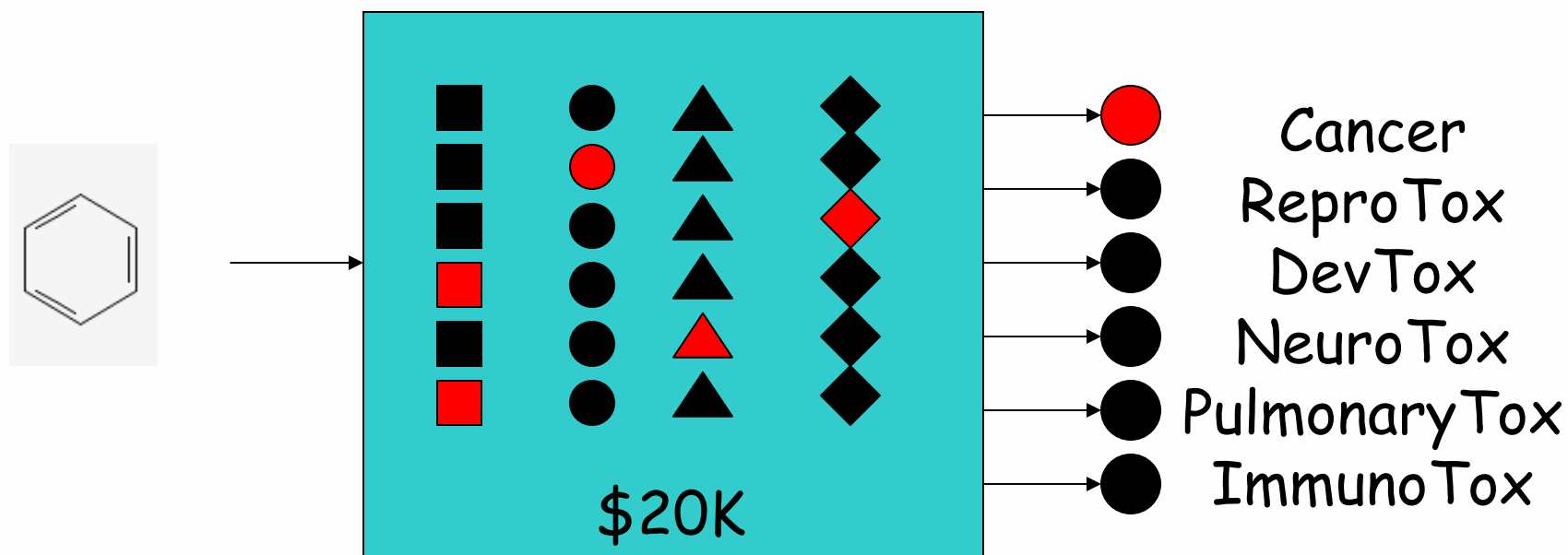
ToxCast™ Merges HTS and Genomics Technologies with Traditional Toxicology



ToxCast™

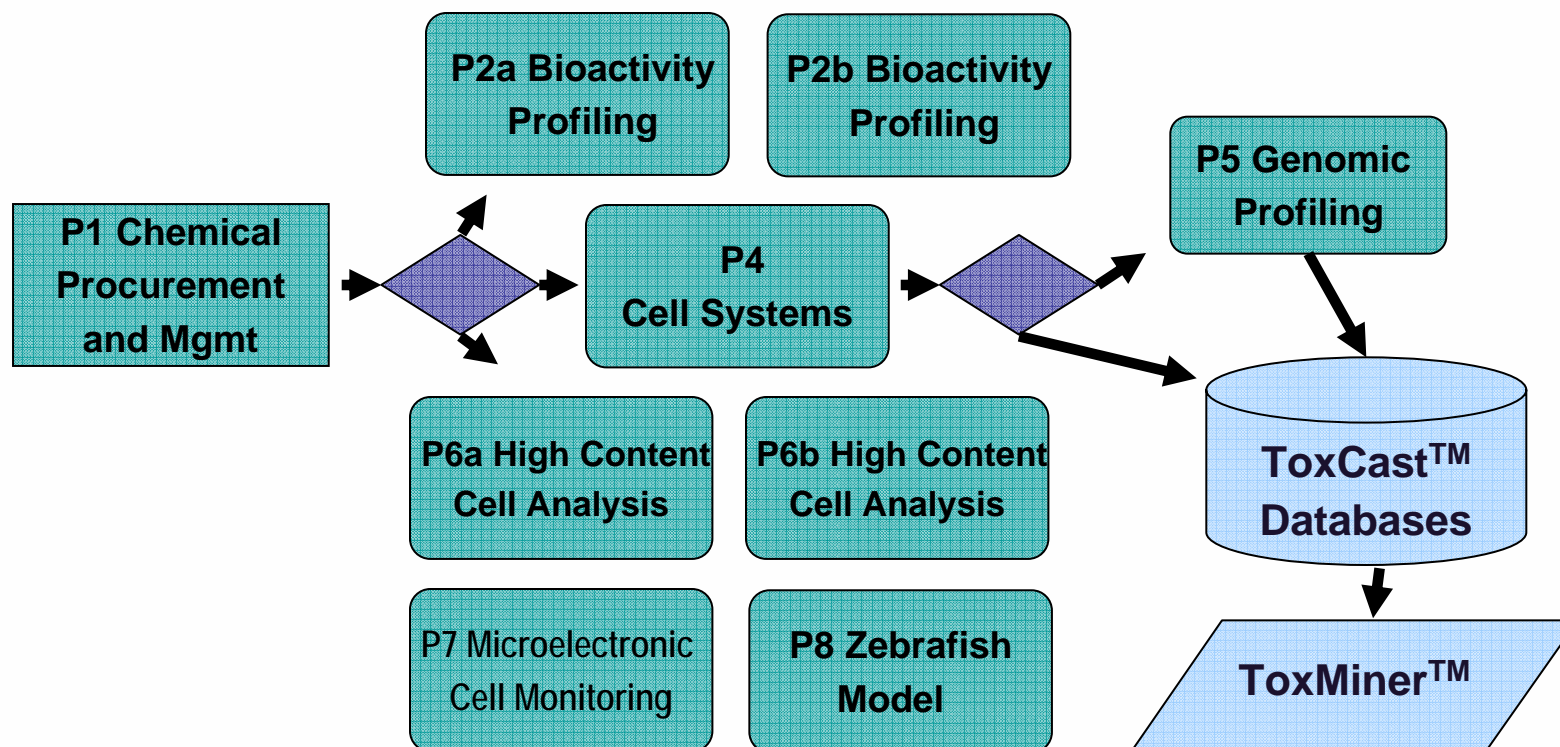


ToxCast™ will identify classifiers or signatures from HTS, HCS and genomics assays to predict hazard...



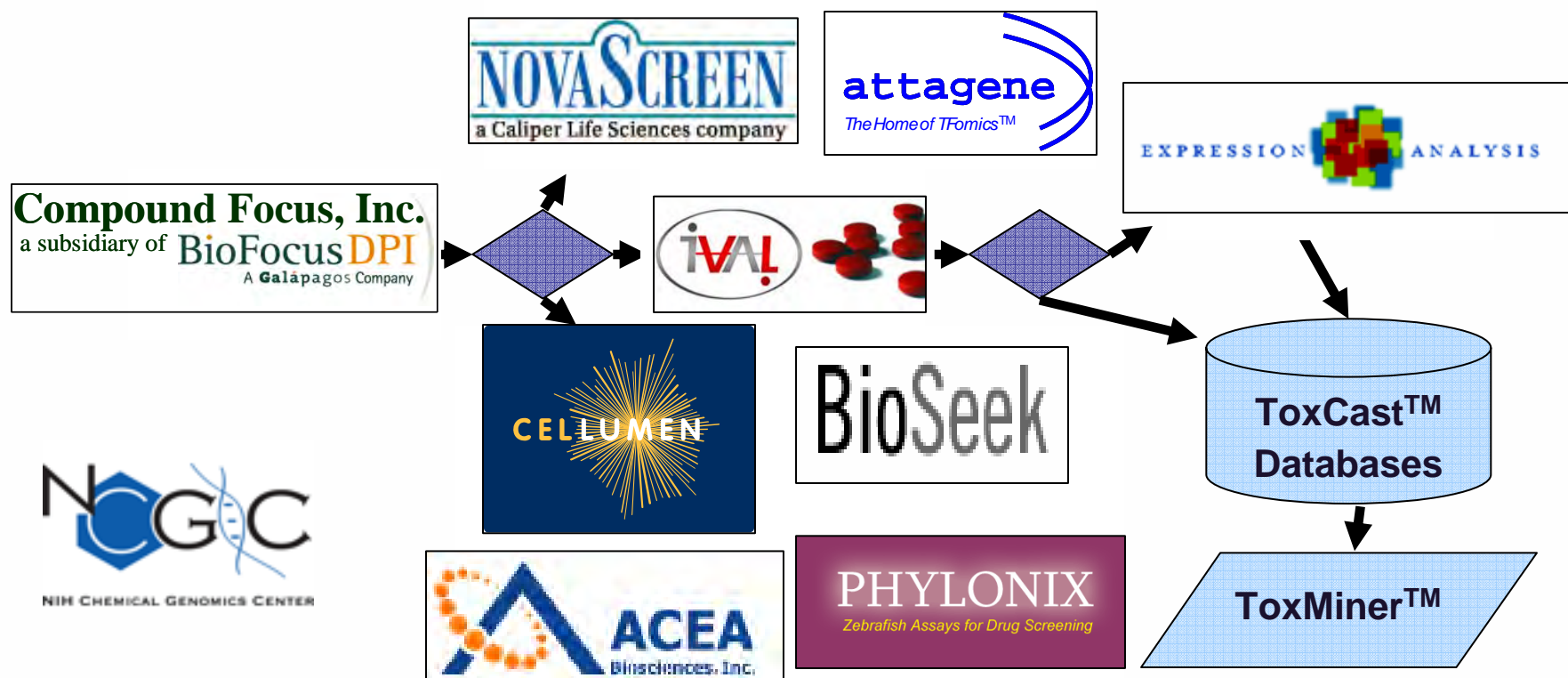
... and prioritize further testing of chemicals.

ToxCast™ Contracts for Data Generation



5yr contracts with flexible quantities and delivery dates of services.

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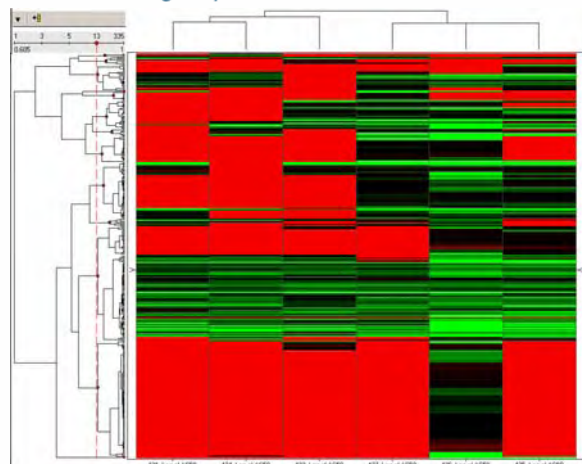
ToxCast:

Pesticides as Proof of Concept

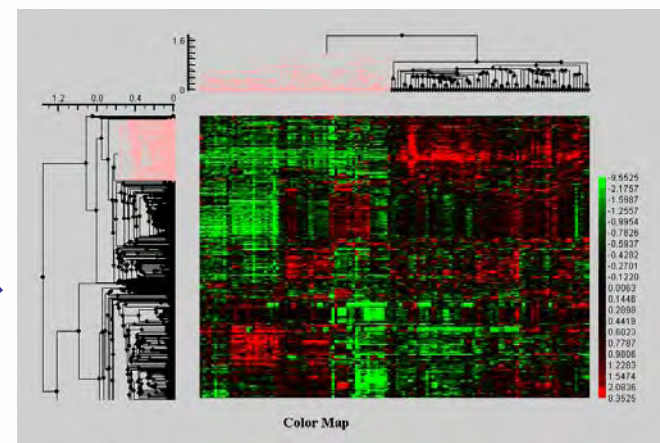
- ~800 Registered in the United States
- Wealth of Toxicological Information (~\$19m)
 - Developmental, reproductive, chronic, etc
- Represent broad range of chemistries
 - Azoles, carbamates, pyrethroids, triazines, etc.
- Designed with biological activity in mind
 - Receptor binding, enzyme inhibition, cytoskeletal, etc.
- Have created a library of 400 for study



Correlating Domain Outputs in ToxCast™



Cellular Assays

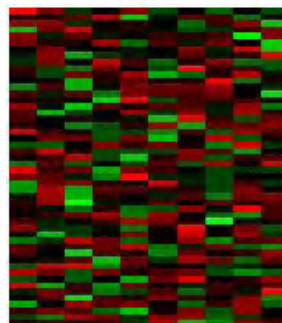


Physical chemical properties

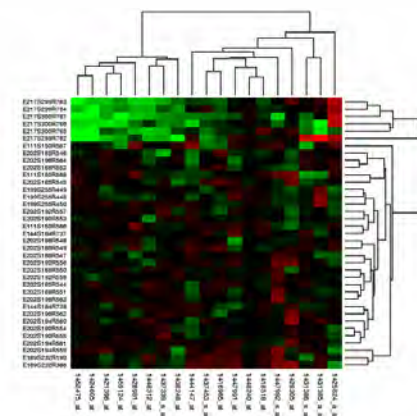
Profile Matching



Biochemical
Assays



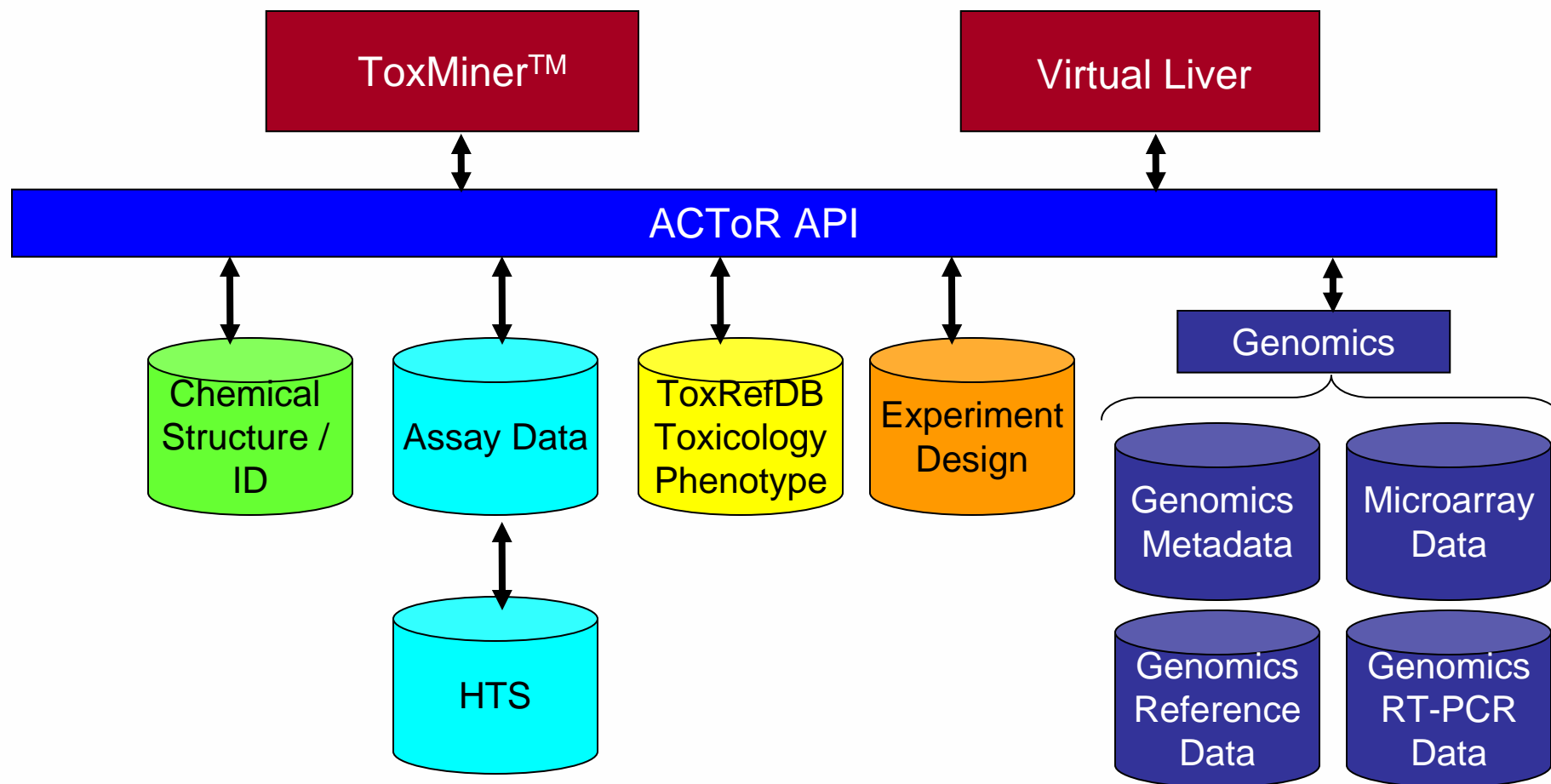
Genomic Signatures



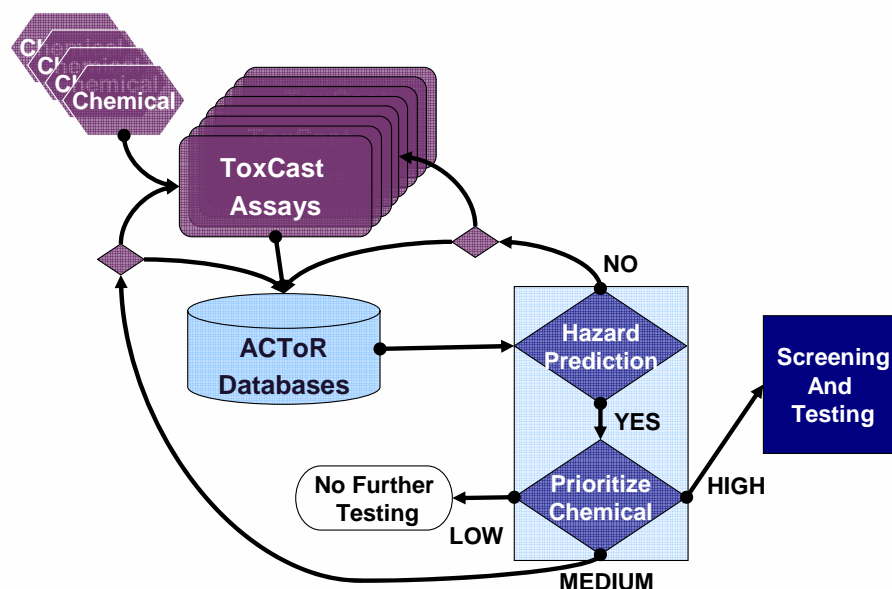
Toxicology Endpoints

ACToR

Aggregated Computational Toxicology Resource



Addresses data needs of ToxCast™ and other EPA programs



Phased Development of ToxCast™

- Phase I: Proof of Concept: derivation of first-generation ToxCast™ signatures based on known toxicity of 300 pesticide actives
- Phase II: Expansion and validation of ToxCast™ signatures with >1000 additional chemicals
- Phase III: Application to thousands of environmental chemicals
 - Deliver affordable, science-based system for categorizing chemicals
 - Identify potential mechanisms of action
 - Refine/reduce use of animals in hazard ID and risk assessment

Roles of ToxCast™ and Virtual Liver Projects in Chemical Prioritization and Risk Assessment

